

STANFORD UNIVERSITY MEDICAL CENTER

DEPARTMENT OF GENETICS

February 3, 1977

Dr. Gustave Silber
Medical Chemistry Study Section
Division of Research Grants -- NIH
Westwood Bldg., Room 357
Bethesda, Md. 20014

Ref: CA 16896-19

Dear Dr. Silber

I am grateful for the opportunity to respond to the study sections's questions about my proposal. In fact I particularly appreciate the 'deferral', since I know how easy it would have been for unresolved questions to result in a pro forma 'approval', with such a qualified priority that the net result would be an unfundable outcome, and disaster for my hopes of continuing this laboratory work.

Appended with this letter are two technical statements:

- 1) a preprint of a paper just submitted to the PNAS on the recent discovery that Staphylococcus plasmids can be transmitted (by straightforward transfection) to Bacillus subtilis.
- 2) the more detailed research plan that was requested. In fact, the plan has had to be revised substantially in the light of (1), a point which may help exemplify some of the more general concerns that I would like to address in this letter.

There are a few very general (and also very personal) points that I ask the study section to have the patience and understanding to consider. Perhaps unlike some of the younger contenders for funds, it is obvious that there are opportunities and calls upon my time other than the continued pursuit of the line of research that I have been connected with since I was a graduate student. That might lead to some confusion about two points that I want to leave in no doubt:

- 1) Without the current grant, I will not be able to continue research in this field, and
- 2) Regardless of other roles that I might play, I place very high importance on continuing that presence, and hope to convince you that I can still make significant contributions in this role.

I have done a great deal of soul-searching about the quality of my commitment, and about the actual pattern of operation that could in practice keep me engaged in a fruitful way. The choice of research area, and the particular style by which I feel I can be most effective, are very closely connected to the substance and the

evolution of this proposal.

In fact, that reflection gave me the cause for the deepest consternation at the request for much more detailed specification of my research plans. As I look back on my earlier work, I have to conclude that ALMOST NONE of the important findings for which I might claim some legitimate pride could have passed muster by this criterion. The original discovery of recombination in *E. coli* is a partial exception -- but even that was an 'unplanned diversion' from a plan to study the (unrealized) possibility of transformation in *Neurospora*. I came to realize (not altogether to my taste) that discovery has been my forte, NOT (sometimes regrettably) the meticulous working out of the details of mechanism of the phenomena I had uncovered. Findings that I could not have specified in advance include the F factor in *E. coli* (the canonical plasmid), lysogenicity (λ) in *E. coli* and its chromosomal localization, replica-plating and indirect selection, transduction in *Salmonella*, and specialized transduction in *E. coli*, the function of penicillin in the inhibition of cell wall synthesis and the formation of spheroplasts; the association of newly synthesized DNA with the cell membrane; and for recent examples, the relation of surface mucopolysaccharide specificity to transfection competence in *Salmonella*, the enhancement of transfection by terminal erosion, and the Staph-to-subtilis transfection mentioned before. This is not a complete catalog of my work: but I have to say that by any objective criterion, my most important contributions have been in the arena of unplanned discovery. The purpose of this recitation is to say something about different styles of science, not just an ego-trip. I understand very well that others have often done a better job of systematic development in areas I had helped to start.

For over five years, the discovery-gamble that most concerned me was the possibility of DNA-splicing; and we know the history: that my associates and I made some pertinent contributions, but we certainly did not win first place in what turned out to be one of the races of the century. Today, we have a rather different outlook than when I first started that line of work.

I have tried to ponder what lessons might be learned from that experience.

One of them, is that the purification and novel applications of enzymes are skills where my colleagues are bound to excel what I can offer. Rather I should stress inquiries that require experience and intuition about what is biologically reasonable to happen with microbes, and experimental methods at that level. If our lab is heavily committed to enzymology much of my relationship to the bench-work would be second-hand, albeit with gifted colleagues like Sgarbetta and Ehrlich -- but their indispensable role would also distance me from first hand confrontation with the experiments.

Planning what to discover is almost a contradiction in terms,

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and may seem an arrogant expectation. Any research program still needs to be self-justifying, but I hope I have been able to convey that its main role is to be a vehicle for continued focussed study, with the expectation that the unexpected would be the most important outcomes. That is also why I am presenting what may seem to be an almost too elementary return to first principles, in the study of bacterial transformation. But this is based on the firm belief that we do not really sufficiently acknowledge what we don't understand about this process which is so fundamentally important both as an experimental methodology, and as a biological process.

The scale of the requested budget and program is, I believe, commensurate with the other statements here; needless to say, like everyone else I recognize I might have to settle for less than the optimal. Frankly, I would prefer a longer commitment, for fewer dollars, than the converse. If I have enough time and the sense of security enough to concentrate on the experimental program, I would have a base from which to look for supplemental funding from other sources -- e.g., NSF. Besides the staff indicated as paid by the grant, I generally have about two graduate students and one postdoc whose stipends come from their own fellowships or from the departmental training grant. I would have welcomed a site visit that could have cleared up possible misconceptions (for better or worse) about the operation of my lab: I realize that, like many other good things of times past that is a forlorn hope.

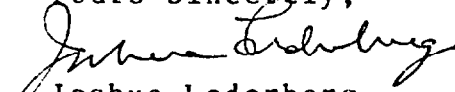
However, there is one point I might stress at the risk of sounding stuffy. I have quite consciously (and sometimes against the requests of my students and fellows) set a policy of NOT putting my own name on papers from my lab unless there was a very strong substantive reason, that went beyond my general oversight, advice and encouragement. This is always a matter of discretion, and I realize it is a different policy than is generally practised in other laboratories; but I think it has also contributed to the morale of younger people who have reason to be concerned about being overshadowed. On the other hand, it may give a false impression about the extent of my personal participation in the work here; since others may interpret bibliographies according to different standards.

On the question of biohazard containment, the staph/subtilis story may mitigate some of the rigor that may have to be imposed; further, some revision of the NIH guidelines may be forthcoming as you know. We are, nevertheless, fortunate to have been able to remodel one of my lab. rooms to P3 standards, which will enable us to work at whatever standard of security is entailed by the guide lines, and by the institutional committee that has local cognizance of these matters. You may not have heard that Stan

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Cohen is joining the Department of Genetics (from Medicine); and I am looking forward to seeing him as a close colleague and neighbor, and he will share the use of this P3 area.

Yours sincerely,

A handwritten signature in cursive script, appearing to read "Joshua Lederberg".

Joshua Lederberg
Professor of Genetics